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Long-Term Efficacy and Safety of Certolizumab Pegol in an Unselected Crohn's Disease Population: The FACTS III Survey

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Keywords
Crohn's disease · Anti-tumor necrosis factor · Certolizumab · Long-term efficacy · Real-life cohort

Abstract
Background: Long-term data of certolizumab pegol (CZP) in Crohn's disease (CD) from pivotal registry trials are limited. We therefore aimed to evaluate the long-term efficacy of CZP in clinical practice in Switzerland. ***Methods:*** In the First Approved Certolizumab Therapeutic Experience in Switzerland-III phase IV multicenter cohort, patients receiving CZP were prospectively included all over Switzerland in (non-) academic hospitals and private practice. ***Results:*** We included 104 CD patients (52 male; only 22.1% anti-tumor necrosis factor (TNF) naïve, CZP as third anti-TNF agent in 46.2%) with follow-up time between 6 weeks up to 5 years. During treatment with CZP, we observed a significant decrease of the Harvey Bradshaw Index from a median of 7 at baseline (interquartile range 4–11) to 4, 5, 4, 3, 3, and 2 at weeks 6, 26, 52, 78, 104, and 156, respectively. While anti-TNF naïve patients showed a significantly better response at the end of induction, during CZP maintenance therapy response was similar as compared to anti-TNF experienced patients as well as between patients with a short (0–5 years) vs. long duration of disease (>5 years). ***Conclusions:*** CZP is an effective long-term treatment option, including CD patients with long disease duration and prior treatment with 1 or 2 anti-TNF agents.

Introduction

The introduction of tumor necrosis factor (TNF)-inhibiting drugs emerged as the beginning of a new era in the treatment of inflammatory bowel disease (IBD) with infliximab in 1997 constituting the first approved agent for the treatment of Crohn's disease (CD) [1]. Shortly thereafter, this pharmacodynamic principle of treatment likewise was approved for ulcerative colitis (UC). Since the beginning of the anti-TNF era, the armamentarium of anti-TNF agents available for CD was always bigger com-

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pared to the one for UC, from the introduction of adalimumab in 2004 [2] – approved for UC only about 7 years later [3] – and shortly thereafter certolizumab pegol (CZP) [4], which never was systematically tested in UC. In contrast, clinicians in most countries of the world are currently faced with the situation that less anti-TNF agents are available nowadays for CD (with 2 agents, namely infliximab and adalimumab), as CZP is approved only in the USA, Russia, and Switzerland. In UC, however, after the recent introduction of golimumab [5], now in most western countries, 3 TNF-inhibitors are approved and available for treatment.

Once the decision to initiate a TNF-inhibiting drug in the treatment of CD patients has been made, there are several reasons to necessitate switching the agent including primary non-response and loss of response (LOR) [1, 2, 4, 6]. This strategy has revealed considerable clinical rates of success [2, 6–8]. Moreover, in clinical practice in a non-negligible fraction of patients, the treating physician is forced to select an alternative TNF inhibitor despite treatment success in view of side effects, such as infusion reactions [9, 10], or paradoxical TNF inhibitor-induced psoriasiform skin lesions [11] (which in some instances may re-occur promptly after a switch to another anti-TNF agent, whereas in other cases can be adequately addressed by switching [12]). Therefore, the availability of a selection of agents within the class of TNF inhibitors is certainly a need for the practicing clinician in the treatment of CD.

While the available data on CZP from PRECiSE I [7], II [13], III [14] found on a robust basis of large randomized and controlled trials, current long-term or clinical real life data are still sparse. Nevertheless, the results from PRECiSE III, a prospective, open-label extension trial, where patients completing PRECiSE II could be included, revealed clinical efficacy of continuous CZP in responders to induction therapy for a maximal observation period of up to 18 months [14] and suggest a therapeutic long-term potential for CZP in CD.

Previously, we reported on the efficacy and safety of CZP induction treatment in an unselected CD patient population in clinical real life, observing rates of response and remission of 54 and 40%, respectively (First Approved Certolizumab Therapeutic Experience in Switzerland [FACTS] survey) [15]. The consecutive extension of the observation period to 6 months identified a sustained clinical efficacy (FACTS II) [16] in this CD population. We herein report on the multicenter long-term observation of CD patients treated with CZP in Switzerland by physicians participating in the FACTS I and II surveys as well as CD patients included thereafter.

Methods

Study Design and Questionnaires

All Swiss gastroenterologists were invited to participate in a questionnaire-based survey of all patients treated with CZP since the first approval of the drug in Switzerland in 2007. We previously reported on the results of induction therapy (FACTS [15]) as well as further clinical course up to week 26 (FACTS II [16]). In accordance to the PRECiSE studies, data were collected at baseline (week 0) directly prior to induction with CZP, week 6 (following induction treatment at weeks 0, 2, and 4) and at week 26 for FACTS I and II. Details on questionnaires have been described previously [15, 16]. We now report on the long-term extension of this survey. All patients included in FACTS I/II were followed up by physician chart review (M.S.). In addition, all gastroenterologists, who included 1 patient, were addressed and further CD patients treated with CZP were included in this long-term analysis. The data collection period lasted from April 3, 2008, to October 30, 2014.

Evaluation of Disease Activity, Efficacy, and Drug Safety Issues

CD activity was measured, in agreement with existing data on CZP, by the Harvey Bradshaw Index (HBI), known to correlate closely with the CD Activity Index (CDAI) [17, 18]. In 2006, Best [19] evaluated the 2 scores by regression modelling and found that a 1-point increase in HBI corresponds to a 27-point increase in the CDAI. According to the European Crohn's and Colitis Organization guidelines for the definition of CD activity [20], we applied the following definitions: an HBI from 0 to 4 points indicates clinical remission (corresponding to a mean CDAI from 26 ± 26 to 134 ± 39), an HBI from 5 to 7 points indicates mild disease (CDAI: 161 ± 42 to 216 ± 49), an HBI from 8 to 15 indicates moderate disease (CDAI: 243 ± 52 to 432 ± 75), an HBI >15 indicates severe disease (CDAI ≥459 ± 78). We defined clinical remission as an HBI ≤4.

The questionnaires assessed frequency and type of adverse reactions and recorded the following items: injection site reaction, allergic reaction outside injection site, headache, gastrointestinal complaints (not CD-related), bleeding, infection, perianal/perineal abscess, and other adverse events. The items were classified according to their probability of being related to CZP into "unclassifiable," "conditional," "unlikely," "possible," "probable," and "certain" according to the WHO definitions of causality assessment [21].

Inclusion and Exclusion Criteria

All CD patients treated with CZP since its approval in Switzerland in September 2007 were eligible, provided that their diagnosis of CD was established on the basis of standard clinical, endoscopic, and histologic criteria at least 6 months prior to inclusion [22]. Patients were excluded if induction treatment with CZP was not performed according to the label (e.g., only 1 CZP injection), which recommends treatment with 400 mg s.c. at weeks 0, 2, and 4.

Statistical Analysis

The statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA) and Prism version 6 (GraphPad Software, La Jolla, CA, USA). Results of quantitative data are presented as median plus interquartile ranges (IQR) for nonparametric data or mean ± SD and range for parametric data, whereas categorical data are summarized as the percentage of the group total. For nonparametric comparisons, the Wilcoxon matched-pairs

signed rank test and Mann-Whitney test were used to analyze paired and non-paired data, respectively. Chi-square testing was applied to test for difference among categorical variables.

Results

Patients Characteristics

A total of 104 patients (52 men) were included with first CZP dose between November 2007 and August 2013 with a follow-up between 6 weeks up to 5 years (median 56 weeks, IQR 26–104) with last evaluation conducted at the end of October 2014. The median age of the patients was 36 years (IQR 29.25–48.75 years) with a median disease duration of 10 years (IQR 3.25–15 years). The majority of patients receiving CZP were experienced to anti-TNF treatment with only 22% previously not having received TNF-inhibiting drugs, thus CZP representing their first anti-TNF agent. While almost half of patients (45%) had previously received infliximab and adalimumab (both are available for the indication CD in Switzerland), 29% had previously been treated with infliximab and 2% with adalimumab only (previous treatment with anti-TFN unknown in 2%). An overview of the most important baseline characteristics as well as previous and ongoing medication use including reasons for cessation is given in Table 1 and Figure 1, respectively.

Evolution of Disease Activity during CZP Treatment and Continuation of Treatment

At baseline, according to HBI, 11.5% had severe (HBI of >15), 26.9% moderate (HBI 8–15), and 26.9% mild disease (HBI 5–7), while 27.9% were in remission (HBI <5). Among the latter group of patients underlying reasons for CZP initiation were either one or a combination of the following factors: previous intolerance/side effects to IFX or ADA (41.4 and 3.4%, respectively), previous surgery (34.5%) and active perianal disease (fistulae and/or abscess, 31%). During treatment with CZP, we observed a significant decrease of HBI from a median of 7 (IQR 4–11) at baseline to 4 ($p = 0.017$), 5 ($p = 0.063$), 4 ($p = 0.002$), 3 ($p = 0.009$), 3 ($p < 0.001$), and 2 ($p < 0.001$) at weeks 6, 26, 52, 78, 104, and 156, respectively. Median HBI remained low at weeks 208 and 260 with 5 and 3, respectively (Fig. 2a). However, due to the small number of patients at these time points (7 and 4, respectively), no significant differences were seen. While the number of patients on CZP progressively decreased during the follow-up time of variable duration, the decreases in HBI translated into increased rates of remission among those

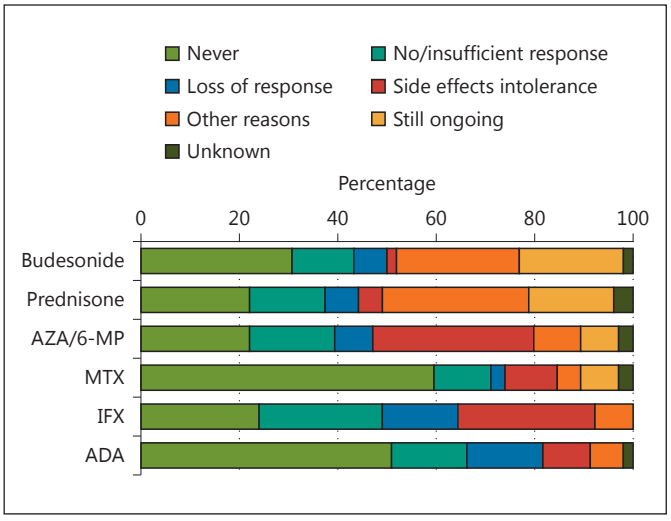

Fig. 1. Previous medication prior to induction with CZP. Prior use of medication is shown including ongoing intake depicted in orange where applicable. Whenever available, reasons for prior discontinuation are provided.

Table 1. Patient characteristics

Gender, male, %	50
Current age, years, median (IQR)	36 (29.3–48.8)
Age at diagnosis, years, median (IQR)	24.5 (19.3–35.5)
Disease duration, years, median (IQR)	10 (3.3–15)
Age at diagnosis (montreal), years, %	
1 (<16)	9.6
2 (17–40)	75
3 (>40)	15.4
Unknown	0
Localization (Montreal), %	
1 (ileal)	13.4
2 (colonic)	63.5
3 (ileocolonic)	21.2
Unknown	1.9
Behavior (Montreal), %	
1 (non-stricturing, non-penetrating)	25
2 (structuring)	25
3 (penetrating)	46.2
Unknown	3.8
Disease duration, years, %	
<1	7.7
1–2	6.7
2–5	12.5
>5	68.3
Unknown	4.8
Previous surgery, %	
No	52.9
Ileal	1.9
Ileal-cecal	26.9
Colonic	9.6
Unknown	8.7
Active smoking, yes, %	33.7

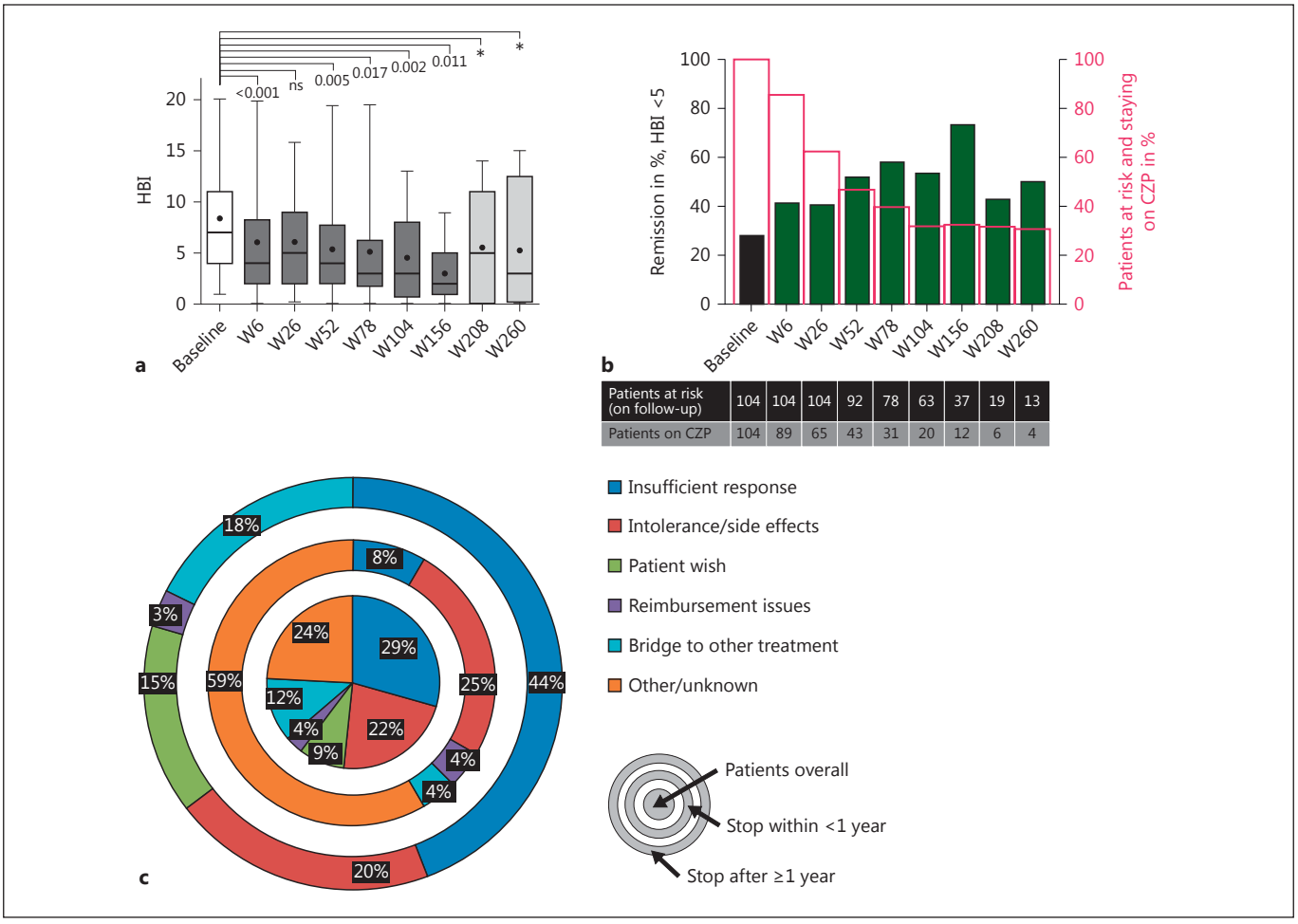

Fig. 2. a–c Evolution of HBI during CZP treatment and reasons for cessation of treatment. Box plots of HBI values at the different times of follow-up are depicted in (**a**) with mean values as black dots within the boxplots (boxes represent IQR, whiskers 5–95 percentile, outliers are not shown). Levels of significance are provided (ns, not significant; asterisks represent small sample size, that is, <10 patients). Corresponding levels of remission during follow-up are provided in (**b**), including the number of patients at risk (at follow-up at) each observational point. The reasons for cessation of CZP administration are depicted in (**c**) for patients overall, as well as according to those patients with early and late treatment withdrawal, defined ad stopping CZP within <1 and ≥1 year after first dose, respectively.

patients with ongoing CZP treatment with 41.4, 40.7, 51.9, 58.1, 53.6, and 73.3% at weeks 6, 26, 52, 78, 104, and 156, respectively, compared to 27.9% at baseline ($p < 0.01$; Fig. 2b). As mentioned above, the duration of follow-up was variable with a shorter interval in those patients included later during the course of the study. At the end of follow-up, 34.6% of patients continued CZP. According to the points in time of evaluation by the physicians, among those patients reaching the weeks 6, 26, 56, 78, 104, 156, 208, and 260, respectively, 85.6, 62.5, 46.7, 39.8, 31.7, 32.4, 31.6, and 30.8% continued CZP treatment (Fig. 2b). An overview on the reasons underlying cessation of CZP administration for patients overall and separated according to early (within <1 year) and late (after ≥1 year) treatment withdrawal is provided in Figure 2c.

Evolution of Disease Activity According to Previous Anti-TNF Treatment and Disease Duration

Comparing HBI in the relatively small subset of anti-TNF naïve patients ($n = 22$) to those previously exposed to 1 or 2 TNF inhibiting agent(s), we did not observe significant differences in baseline disease activity. However, TNF naïve patients revealed to have a significantly better treatment response directly after induction therapy at week 6 ($p = 0.001$). During complete follow-up

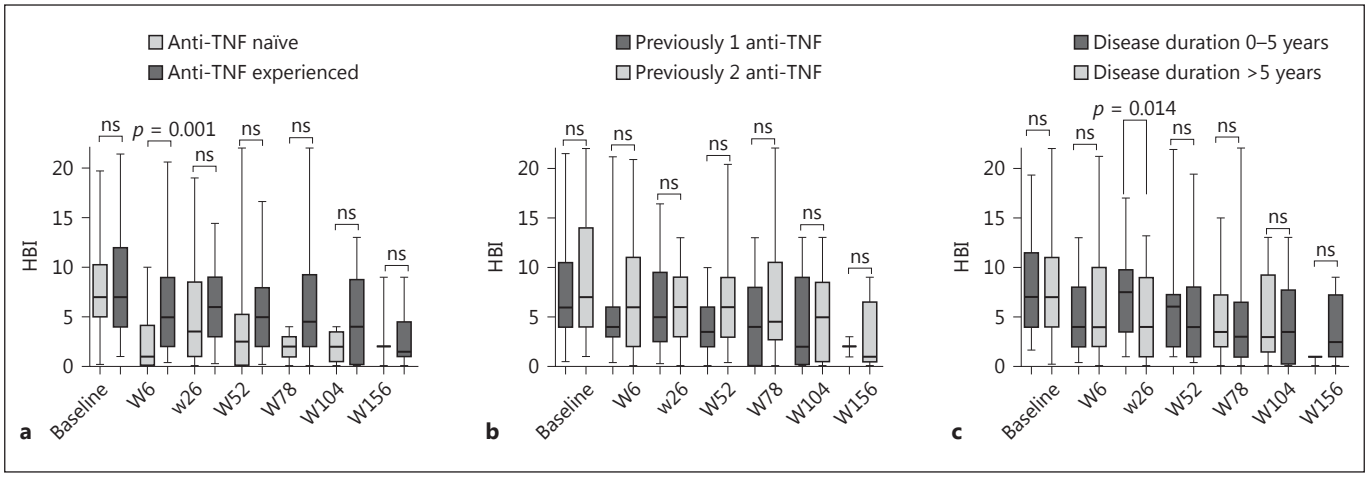

Fig. 3. a–c Evolution of HBI during CZP treatment according to subgroups. Box plots of HBI values at the different times of follow-up are depicted (with black lines as mean values) for anti-TNF experienced vs. naïve (**a**) patients, patients previously treated with 1 vs. 2 anti-TNF agents (**b**), and patients with a disease duration of 0–5 vs. >5 years (**c**).

treatment, response in TNF naïve patients also tended to be better compared to their counterparts previously having received anti-TNF treatment. However, this difference was not significant (Fig. 3a). Treatment duration in the anti-TNF naïve patients was not higher compared to patients previously treated with TNF inhibitors. Indeed, in the latter, mean treatment duration was even higher with 73.8 vs. 67.5 months ($p < 0.001$). Next, we aimed to investigate whether response to CZP differed for patients with previous exposure to 2 anti-TNF agents compared to those having received only one agent. Although disease activity was higher at baseline in the former group only a slight trend toward higher activity remained at the end of the observation period and this difference was not significant (Fig. 3b). Moreover, we compared disease activity during CZP induction and maintenance between patients with a shorter (0–5 years) vs. longer (>5 years) disease duration. While HBI was similar at baseline and after induction (week 6) between both groups of patients, response after 6 months of treatment was significantly better in the long vs. short disease duration patients corresponding to a median HBI of 7.5 vs. 4 ($p = 0.014$). This was also seen at week 52 and 78 by trend with however no significant difference (Fig. 3c).

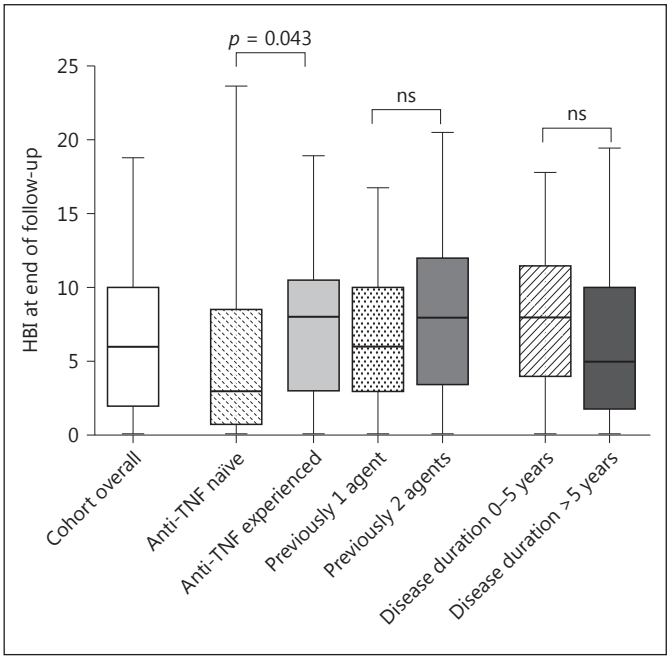

Fig. 4. HBI at end of follow-up. Box plots of HBI values at the last point of follow-up for the cohort overall and according to the subgroups mentioned in the legend for Figure 3.

Disease Activity at End of Follow-Up

At the last follow-up evaluation, which occurred at a median of 56 weeks after the initiation of CZP induction treatment (IQR 26–104 weeks), the median HBI at end of follow-up was significantly lower in anti-TNF naïve patients (3 vs. 8 in patients previously having received anti-TNF, $p = 0.043$; with a median HBI of 6 in the cohort overall). In contrast, no significant differences were observed within the anti-TNF experienced patients between those previously having received 1 vs. 2 agents as well as between patients with a disease duration of 0–5 vs. >5 years (Fig. 4).

Table 2. Adverse events according to weak of treatment are depicted

	Injection site reaction	Allergic reaction outside of injection site	Headache/ migraines	Gastrointestinal (not Crohn's worsening)	Bleeding	Infection	Perineal/ perianal abscess	Other
W6								
Definite	1 (1)	3 (2,9)	1 (1)	–	–	–	–	4 (3.8)
Probable	–	2 (1.9)	–	–	1 (1)	–	–	2 (1.9)
Possible	1 (1)	2 (1.9)	1 (1)	6 (5.8)	1 (1)	3 (2.9)	–	3 (2.9)
Sum	2 (1.9)	7 (6.7)	2 (1.9)	6 (5.8)	2 (1.9)	3 (2.9)	–	9 (8.7)
W26								
Definite	1 (0)	1 (1.1)	1 (1.1)	–	–	1 (1.1)	–	1 (1.1)
Probable	–	1 (1.1)	2 (2.2)	–	–	1 (1.1)	–	3 (3.3)
Possible	–	2 (2.2)	1 (1.1)	4 (4.4)	1 (1.1)	2 (2.2)	–	5 (5.5)
Sum	1 (0)	4 (4.4)	4 (4.4)	4 (4.4)	1 (1.1)	4 (4.4)	–	9 (9.9)
W56								
Definite	–	–	1 (1.9)	–	–	–	–	1 (1.9)
Probable	–	–	–	1 (1.9)	–	–	–	1 (1.9)
Possible	–	–	1 (1.9)	2 (3.8)	–	–	2 (3.8)	3 (5.8)
Sum	–	–	2 (3.8)	3 (5.8)	–	–	2 (3.8)	5 (9.6)
W78								
Definite	–	–	–	–	–	–	–	1 (3.2)
Probable	–	–	–	–	–	–	–	–
Possible	–	–	–	–	–	–	–	1 (3.2)
Sum	–	–	–	–	–	–	–	2 (6.5)
W104								
Definite	–	1 (3.6)	–	1 (3.6)	–	–	–	1 (3.6)
Probable	1 (0)	–	–	–	–	–	–	–
Possible	–	–	2 (7.1)	–	–	1 (3.6)	–	–
Sum	1 (0)	1 (3.6)	2 (7.1)	1 (3.6)	–	1 (3.6)	–	1 (3.6)
W156								
Definite	–	–	–	–	–	–	–	–
Probable	–	–	–	–	–	–	–	–
Possible	–	1 (6.7)	–	1 (6.7)	–	–	–	1 (6.7)
Sum	–	1 (6.7)	–	1 (6.7)	–	–	–	1 (6.7)

Each occurrence of an adverse event was rated by the treating physician as definite, probable, possible or not related to the administration of CZP. Those events not considered to be related to the drug are not shown here. Crude number for any adverse event given are depicted according to the likelihood of relation to drug exposure including the sum of the 3 categories.

In brackets, percentage for any adverse event according to the patient number at risk at any given observational point are shown.

At end of follow-up, CZP was continued in 36 patients (i.e., 34.6% of all patients included) with no significant differences between anti-TNF naïve (30.4%) and experienced (overall: 35.8%; one previous agent: 34.4%, 2 previous agents: 36.7%) and those patients with a shorter (0–5 years, 24.2%) vs. longer disease duration (>5 years, 39.4%, ns).

Safety and Adverse Events

No events of tuberculosis, cancer, lymphoma, or death were reported. An overview on the nature, time points, and frequencies (both absolute numbers and in percentage of patients at risk at each given time point) of reported adverse events is provided in Table 2. Allergic reactions reported included pruritus, increase of arthralgia, exanthema including 1 case of a possible pityriasis rosea, and injection site reactions with local redness, itching, and pain. None of these led to cessation of the drug. However, there was one 30-year-old male patient developing severe limb pain, fever, dyspnoea, nausea, myalgia, and a full body exanthema classified as probably related to CZP and entailing stop of the agent at week 6. Furthermore, a 36-year-old female patient developed progressive myalgia in the extremities (again rated as probable related to CZP), also resulting in CZP withdrawal at week 104. Infections observed were cases of urocystitis, sinusitis, and bronchitis. In addition, single cases of bacterial vaginosis,

enoral infection of a tooth, herpes labialis, skin abscess as well as an infection of a port-a-cath were reported. Gastrointestinal symptoms including constipation, meteorism, nausea, and vomiting were felt to be at least possibly related to CZP administration. Two patients reported some irregularities with menstrual cycle and menometrorrhagia. Other adverse events with possible, probable, or definitive causal association to CZP were paresthesia, fatigue, hair loss, dry eyes, psoriasiform skin reaction, muscle cramps, dysgeusia, night sweat, depressive symptoms, and edema.

Discussion

In this open-label multicenter observational study, we report on the results of long-term treatment with CZP in CD in a clinical real-life setting with participating gastroenterologists from private practice and academic as well as non-academic medical centers in Switzerland. Our results demonstrate that CZP is an effective long-term treatment option to achieve and maintain clinical response and remission in an unselected and vastly treatment-experienced CD patient population.

Until now, there was a lack of clinical long-term data with CZP beyond a treatment period of 6 (PRECiSE II [13] and FACTS II [16]) and 18 (PRECiSE III [14]) months, respectively. In view of this and the well-established considerable LOR rates with anti-TNF-agents, particularly within the first year of treatment, yet also continuously thereafter [6] long-term data are important for the practicing clinician involved in the care of CD patients. In congruence with the clinical experience with other agents, in our cohort, the fraction of patients with cessation of CZP is highest within the first year of treatment. However, our data with an observational period of up to 5 years indicate that those patients staying on the drug beyond 12–18 months experience a sustained clinical benefit. The rates of treatment cessation may appear high in our cohort. However, besides the fact that our patient cohort was highly treatment experienced with almost every second patient having received CZP as the third anti-TNF agent, a similar fraction of patients remained on CZP after 26 weeks compared to PRECiSE II, that is, 62.5% in our cohort vs. 69.9% in PRECiSE II (here, however, only those roughly two-thirds of patients responding to induction treatment were considered for maintenance therapy) [13]. Both, this selection of responders after induction and also the intermittent placebo phase between weeks 6 and 26 in the design of PRECiSE II in conjunction with the baseline characteristics with less than 20% of patients with prior infliximab exposure (and none with previous treatment with adalimumab) in rigorous contrast to our extensively anti-TNF-experienced cohort precludes a decent comparison of our data to the results from PRECiSE III [14]. Nevertheless, our results clearly imply that CZP is a valuable and effective long-term treatment option for a substantial fraction of – even difficult-to-treat – CD patients. Moreover, the long-term safety profile of CZP appears to be favorable with a frequency of mild-moderate (and no severe) adverse events as expected from the previous literature in the first months of treatment and only few incidents thereafter [23–26].

As expected, naïve patients (the vast minority in our study, only 1 in 5 patients) had a significantly better response after induction at week 6. However, in the further course of treatment, no significant differences in clinical benefit were observed according to prior anti-TNF exposure. In general, in virtually all biological agents tested in IBD and even in the emerging small molecules, efficacy rates were found to be higher in anti-TNF naïve patients as compared to those with previous exposure. Underlying reasons for this difference remain somewhat elusive. The traditional and often reported explanation considers previous anti-TNF exposure being a surrogate marker of a more severe course of disease and also one that is more difficult to therapeutically address. However, as the interpretation of the investigators conducting the phase II trial of ustekinumab [27] illustrates, explanations may be primarily driven by the results obtained at that time point and not necessarily by a critical review of the available overall evidence. Initially, a presumable superiority of this agents in patients previously exposed to infliximab – at that time explained by an alternate immunological pathway (i.e., for instance rather TH17 than TNF-α) in this subgroup of patients – was refuted in the subsequent phase III study [28], revealing significantly superior efficacy rates in anti-TNF naïve CD patients, leading to a renaissance of the traditional explanation (previous anti-TNF exposure = indicative of a generally more severe course of disease). Interestingly, the phase II ustekinumab had an identical number of participating patients as our long-term observational study (104 patients). This example illustrates that conclusions on diverging efficacy between subgroups of patients in such a relatively small patient number have to be drawn with great caution and may be misleading if subsequently tested in a larger patient group. Therefore, we cannot definitely state whether there indeed may be a difference as compared to inflix-

imab or adalimumab, in that efficacy rates in naïve vs. previously exposed align on the long-term to a comparable overall efficacy, or whether this observation rather is erroneous, as for instance due to a small case number or a potential source of bias.

As total CZP treatment duration was not shorter in the experienced group of patients (indeed a longer overall mean treatment duration was seen in our cohort), this beneficial effect cannot be explained by a bias due to preferential premature treatment withdrawal in anti-TNF-experienced patients. Accordingly and despite the words of caution expressed in the previous sentences, one of the key findings of our study is the sustained clinical long-term benefit of CZP also in CD patients previously having received infliximab or adalimumab and even both agents.

The clinical benefit regardless of disease duration observed in our cohort appears to be in contrast to the previous literature with adalimumab [29, 30], certolizumab [31], and infliximab in children [32], all of which suggest better response rates with shorter disease duration. In adults, however, response rates of infliximab did not appear to be associated with disease duration [33–35].

Recently, retrospective long-term data on the efficacy of CZP were reported and identified early age of CD manifestation, previous primary non-response to adalimumab, and presence of perianal fistulizing disease as negative predictors of response [36]. However, these patients represent a highly selected collective from a single large US tertiary referral center. In contrast to these single-center results, neither younger age nor prior treatment with adalimumab nor presence of fistulizing disease was associated with a premature stop of CZP in our cohort (mean patient age 41.1 years, 50% B3 disease and 47.2% without prior adalimumab exposure in those patients still on CZP at last follow-up vs. 37.1 years, 44.1% B3 and 52.9% without prior adalimumab in those patients where CZP was withdrawn).

The availability of a selection different TNF-inhibiting agents represents an important clinical need due to several reasons including primary non-response [1, 2, 4, 6] LOR [6] (where switching within class has revealed been to be a highly successful and safe option [2, 6–8]), and not terribly intriguing reported success rates of newly available or emerging treatment options. Moreover, the field of emerging treatment options in IBD currently appears to be evolving somewhat less impressively in CD as compared to UC and those targets that are investigated in UC and CD, such as strategies addressing leucocyte migration or inhibition of JAK/STAT activation, seem to work better in the former.

An important limitation of our study is the variable follow-up time per patient with only small patient numbers at the longest observational points. Moreover, endoscopic data or fecal calprotectin levels to undermine the clinically derived response were not available. Furthermore, predefined criteria for stopping the agent for uniform clinical practice were lacking. Strengths of our study include the long-term follow-up, the multicenter setting including gastroenterologists in private practice as well as academic centers, and the unselected study population with a high rate of previous anti-TNF exposure. Our study may thus represent a real-life scenario with difficult-to-treat CD patients.

In summary, we identified CZP as an effective long-term treatment option in CD patients regardless of the duration of their disease as well as prior exposure and clinical response to 1 or 2 anti-TNF agents in our long-term observational study. Accordingly, and in view of the still limited alternative treatment options for CD patients with an insufficient response to infliximab and/or adalimumab, we conclude that there is definitely a place and also a need for a third TNF-inhibiting agent in the treatment of CD.

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Ethics Statement

The survey represents a nested project of the Swiss IBD Cohort Study and was approved by the Ethics Committee of Lausanne University Medical Center.

Disclosure Statement

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Author Contributions

S.R.V., G.R., P.M., A.M.S., F.S., and A.S. formed the concept of the study. J.B. and C.M. performed pre-evaluations for data extraction from the patient charts. M.S. performed the data extraction from patient charts in cooperation with L.B., P.M., P.F., A.S., J.B., F.S., and J.Z. L.B. carried out first analyses of data together with M.S., T.G., C.M., and S.R.V. L.B. performed the statistical analysis together with B.M., S.R.V., and M.S. L.B. wrote the draft of the manuscript, with critical input of G.R., S.R.V., B.M., and J.Z. All co-authors read the manuscript and provided important contributions for the overall quality with ultimate approval of the final manuscript.

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